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IMPACT OF LOCATION ON PLACENTATION IN LIVE TUBAL AND CESAREAN SCAR ECTOPIC PREGNANCIES

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Abstract:	Introduction: The objective of this study was to evaluate the impact of implantation outside the normal intra-uterine endometrium on development of the gestational sac. Methods: We reviewed and compared the ultrasound measurements and vascularity score around the gestational sac in 69 women diagnosed with a live tubal ectopic pregnancy (TEP) and 54 with a cesarean scar ectopic pregnancy (CSP) at 6-11 weeks of gestation who were certain of their last menstrual period. Results: The rate of a fetus with a cardiac activity in the study population was significantly (P <.001) higher in CSPs than in TEPs. The median maternal age, gravidity and parity were significantly (P =.005; P <.001 and P <.001, respectively) lower in the TEP than in the CSP group. The number of gestational sac size < 5 th centile for gestational age was significantly (P <.001) higher in the TEP than in the CSP group. There were no differences between the groups for the other ultrasound measurements. In cases matched for gestational age, the gestational sac size was significantly (P <.001) smaller in the TEP compared to the CSP group. There was a significant (P <.001) difference in the distribution of blood flow score with CSP presenting with higher incidence of moderate and high vascularity than TEP. Discussion: Both TEP and CSP are associated with a higher rate of miscarriage than intrauterine pregnancies and the slow development of the gestation sac is more pronounced in TEPs probably as a consequence of a limited access to decidual gland secretions.
Suggested Reviewers:	Ron Maymon Professor, Tel Aviv University maymonrb@bezeqint.net Was one of the first to publish on ectopic pregnancies including scar pregnancies (see Ref 6).
	Ana Idelson Tel Aviv University Sackler Faculty of Medicine idelsondoc@gmail.com Has published an article recently on "New predictors of early impaired placentation preceding miscarriage before 10 weeks of gestation in IVF pregnancies: A prospective study. Placenta. 100 (2020) :30-34.

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Abstract **(word count 250)**

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Discussion: Both TEP and CSP are associated with a higher rate of miscarriage than intrauterine pregnancies and the slow development of the gestation sac is more pronounced in TEPs probably as a consequence of a limited access to decidual gland secretions.

HIGHLIGHTS

- Live tubal and cesarean scar ectopics have a high rate of miscarriage at 6-11 weeks
- Reduced gestational sac diameter is the first ultrasound sign of pregnancy failure
- Tubal pregnancies have limited access to intrauterine histiotrophic support
- Cesarean scar ectopics develop close the normal intrauterine environment
- Tubal ectopics are less likely to progress into the second trimester

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1.Introduction

Ectopic pregnancy is defined as the implantation of an 7-8 days post-fertilization blastocyst outside the uterine endometrium [1,2]. Ectopic pregnancy affects around 2% of spontaneous pregnancies and up to 5 % of pregnancies resulting from assisted reproductive technology (ART). The most common extrauterine location is the Fallopian tube, predominantly the ampullary region, which accounts for more than 90 percent of all ectopic gestations. Implantation in the cervix, ovary, myometrium (intramural) and abdominal cavity are rare and collectively account for less than 10 % of ectopic pregnancies.

Tubal ectopic pregnancies (TEPs) have been known to modern medicine for over 100 years [3]. By contrast, cesarean scar pregnancy (CSP) is a newly described type of ectopic pregnancy [4]. Early studies have estimated the incidence of CSP to be 1:1800 to 1:2216 (0.05–0.04%) pregnancies, representing 4% of all ectopic pregnancies [5,6]. A recent national cohort study using the United Kingdom (UK) Early Pregnancy Surveillance Service (EPSS) has shown that the incidence of CSP is around 1.5 per 10,000 maternities [7]. There is also mounting evidence that a CSP can evolve into a placenta accreta [8-11]. As cesarean delivery rates continue to rise [12], it is likely that the incidence of CSP will continue to increase in the next decade.

TEPs are mainly secondary to a damage to the Fallopian tubes, usually due to inflammation which induces tubal dysfunction and can result in retention of an oocyte or embryo [1], whereas CSPs are exclusively due to the presence of a myometrial scar following a cesarean section delivery [8-11]. There are similarities between tubal pregnancies where the blastocyst implants within the epithelium of the Fallopian tube and cesarean scar placentation. Histopathological studies have shown that extravillous trophoblastic cells invade tubal vessels but subsequent development of the placenta in the tube differs from that in the uterus, in so far as invasion of the tubal tissues is unrestrained, with penetration of the trophoblast into the tubal serosa [13]. Similarly, there is often an absence of re-epithelialisation in large uterine scar area [14] and the myometrial scar tissue often presents with myofibre disarray, tissue edema, inflammation and elastosis [15]. This allows the extravillous trophoblastic cells to invade beyond the inner third of the myometrium, also called the junctional-zone, and reach vessels in the outer myometrium [16].

Little is known about the impact of different implantation environments outside the normal uterine endometrium on placentation and subsequent development of the gestational sac. The objective of this study was to compare the early development gestational sacs in the Fallopian tube and in a prior cesarean scar to better understand the pathophysiology of both conditions and contribute to the counselling women about the risks associated with different management strategies.

2.Materials and methods

Patients diagnosed with a live TEP or a live CSP included in the present study were recruited from a cohort of pregnant women attending the early pregnancy assessment unit (EPAU) at University College London Hospital (UCLH) over an 8 year-period ending December 2019. Patient's demographic data, previous obstetric and gynecological history, clinical findings, ultrasound data and images and symptoms at the time of the first examination were recorded and stored in a specialized database (Viewpoint Version 5, Bildverargeritung GmbH, Munich, Germany). Pregnancies were dated according to the last menstrual period (LMP). Only women who were certain of their LMP were included in the study groups. Data on the mode of conception were not recorded consistently in the questionnaires as optional for the patient to report. Patients with multiple pregnancies including heterotopic pregnancies were excluded from the final analysis.

Ethical committee approval (UK NHS Health Research Authority (HRA) Research Ethical committee approval reference 18/WM/0328) was obtained prior to the start of this study. The protocol and a waiver of consent were granted a favorable opinion as all ultrasound records were examined within the center and basic clinical data were collected using a standard clinical audit protocol.

2.1 Ultrasound examination

All ultrasound examinations were carried out transvaginally and/or transabdominally by experienced operators using a high-resolution ultrasound equipment (Voluson 730 and E8 Expert, GE Medical Systems, Milwaukee, WI, USA). Implantation of a gestational sac within a previous caesarean section scar was diagnosed according to the criteria previously described [5].

Viability of the pregnancy was confirmed by visualization of the embryonic or fetal pole with evidence of cardiac activity on transvaginal scan. Measurements obtained during the scan included gestational sac diameter (GSD) calculated as the mean of 3 orthogonal planes, crown-rump length (CRL), fetal heart rate and secondary yolk sac size. The corresponding centiles were evaluated using previously published normograms for singleton pregnancies at 6-10^{+6} weeks of gestation [17]. The presence of a hemoperitoneum was noted. Color Doppler imaging (CDI) with a default pulse repetition frequency of 0.9 kHz, gain of 0.8 and low wall motion filter (40 Hz) was used to assess the vascularity around and within the gestational sac. A semi-quantitative color score method with a scale from 1 to 4 was used to record peri-gestational sac blood supply as previously described [18]. In brief, a score of 1 was given when there was no detectable blood flow, of 2 for minimal blood flow present, of 3 for moderate blood flow and of 4 for high vascularity (Fig. 1).

2.2 Statistical analysis

StatGraphic-plus Version 3 data analysis and statistical software package (Manugistics, Rockville, MD) was used to analyse the data. A standard Kurtosis analysis indicated that some values were not normally distributed and the data are therefore presented as median and interquartile range (IQR). To evaluate the effect of the ectopic pregnancy location on ultrasound parameters, data from the TEP and CSP groups were matched for days of gestation. Both study groups were subdivided according to gestational age i.e. < 50 days (n=20) and $\geq$ 50 days (n=20). Categorical variables were compared between groups and subgroups using the Pearson's chi-square test or Fisher's exact test when samples sizes were small. Continuous variables were compared using a Mann-Whitney (Wilcoxon) W rank test at the 95% confidence interval (CI). A *P* value <0.05 was considered significant.

We used SigmaPlot 13.0 (Systat Software Inc, San Jose, CA) to create plots of mean GSD versus time (days). We then used the curve fit function to fit quadratic equations to evaluate the mean GSD over time in both groups.

3. Results

3.1 Study population demographics

During the study period, 1,479 pregnant women were diagnosed with an ectopic pregnancy including 1,226 TEPs, 238 CSPs, nine ovarian, three abdominal, two cervical and one intramural. The rate of a fetus with a cardiac activity at 6-11 weeks of gestation was significantly (P <.001) lower in TEP (92/1241; 7.3%) than in the CSP (80/238; 33.6%).

3.2 Study groups demographics

In the live TEP group with certain last menstruation date (n= 69), eight (11.6%) women presented with a history of one or more prior cesarean deliveries, six (8.7%) had had a previous TEP and 27 (39.1%) had had one or more surgical dilatation and curettage (D&C)

for early pregnancy failure, pregnancy termination or both. There were 35 gestational sacs located in the left Fallopian tube and 34 in the right tube. The presence of hemoperitoneum was recorded on transvaginal ultrasound examination in 21 (30.4%) cases.

In the live CSP group with certain last menstruation date (n= 54), the median number of prior cesarean deliveries was 2.0 (IQR 1;2). Three (5.6%) women had a history of a previous CSP and three (5.6%) had a prior TEP. There were 29 women (53.7%) who had one or more D&C for early pregnancy failure, pregnancy termination or both. There were no cases of hemoperitoneum in this group.

The maternal demographics of both study groups are compared in Table 1. The median maternal age, gravidity and parity were significantly (P =.005; P <.001 and P <.001, respectively) lower in the TEP group than in the CSP group. There was no significant difference in the gestational age at diagnosis. Thirty-two (46.4%) women in TEP and 15 (27.8%) in CSP groups respectively were asymptomatic at the time of their transvaginal ultrasound examination. The distribution of women presenting with bleeding, pelvic/abdominal pain or both was not significantly different between the two groups.

3.3 Comparison of the ultrasound characteristics of both study groups

The number of GSD < 5^{th} centile was significantly (P <.001) higher in the TEP group than in the CSP group (Table 1). There were no differences between the groups for the other ultrasound measurements. There was a significant (P <.001) difference in the distribution of blood flow score between the groups, with the CSP group presenting with higher incidence of moderate and high vascularity than the TEP group.

Figure 2 presents the changes in gestational sac size with advancing gestation. The equation for tubal ectopic pregnancy group mean GSD over time was GSD= 59.47 + -2.0314*GA+0.0221*GA^2 (R^2=0.3410). The equation for the cesarean scar pregnancy group mean GSD over time was GSD = -7.6550 +0.3980*GA+0.0031*GA^2 (R^2=0.5545). Table 2 compares the median ultrasound measurement in TEP and CSP groups matched for gestational age. The GSD was significantly (*P* <.001) smaller in the TEP group compared to the CSP group. There was no significant difference for the other parameters. In the gestational age subgroups, a significant; (P =.002) difference was found for the GSD in pregnancies of < 50 days (median 9.2mm (IQR 6.8;12.2) for TEPs median *versus* median 16.5mm (IQR 11.5;22.2) for cesarean scar pregnancies; W 83.5; P <.002) but not for pregnancies of $\geq$ 50 days. There was no significant difference for the other parameters.

4. Discussion

To our knowledge this is the first study that has been carried out to assess and compare the development of pregnancies implanted in a Fallopian tube and in a cesarean scar. Early pregnancy loss within 12 weeks and 6/7 days of gestation affects around 10% of all clinically recognized pregnancies [19,20]. Our data indicates that both TEP and CSP are associated with a higher rate of early pregnancy failure than intrauterine pregnancies with < 10% of TEPs and around 1/3rd of CSPs presenting with a fetal cardiac activity at 6-11 weeks' gestation.

Ultrasound measurements of the gestational sac, fetal length, fetal heart rate and secondary yolk sac have been used for over two decades to predict the risk of subsequent miscarriage in live normally implanted intrauterine pregnancies at 6-10 weeks' gestation. Overall, in women with known last menstrual period in spontaneous pregnancies or known date of ovulation or embryo transfer in pregnancies resulting from ART, a smaller than expected GSD has been reported by all authors as predictive of subsequent miscarriage despite a normal fetal cardiac activity [21-27]. Smaller CRL [22,28] and lower fetal heart rate (24,28,29] for gestational age have also been reported in pregnancies that subsequently miscarried whereas in those cases the yolk sac size has been described as normal [24], decreased [29] or increased [25,30,31]. The gestational sac and yolk sac sizes starts deviating from normality as early as 6 weeks of gestation followed by changes in CRL and fetal heart rate at 7 and 8 weeks [26]. In the present study, we found a significantly (P <.001) higher incidence of GSD < 5th centile for gestational age (Table 1) and median gestational sac size (Table 2) in TEPs than in CSPs. This difference was only observed in matched cases for pregnancies < 50 days. CRL measurements were also smaller in TEPs than in CSPs but the difference was non-significant whereas the distribution of abnormal measurements for the other ultrasound parameters was similar between the study groups.

The frequency of clinically recognized early pregnancy loss increases with advancing maternal age due to a higher incidence of aneuploidy in older mothers [32]. In the present study, the maternal age was significantly (P <.001) higher in the CSP group than in the TEP group suggesting that the former group should have a higher incidence of early pregnancy failure due to aneuploidies. A small for gestational age CRL in a first-trimester live fetus has been associated with an increased risk of chromosomal anomalies, in particular monosomy X and trisomy 21 at 6-10 weeks' gestation [33] and trisomy 18 and triploidy at 11-14 weeks [34]. There are limited data from small studies on the incidence of aneuploidy in TEP showing a higher rate of chromosomal abnormalities compared to normally implanted intra-uterine pregnancies [35,36]. There are no data on the incidence of aneuploidy in CSP, however, the above findings suggest that the difference in miscarriage rate between TEP and CSP is unlikely to be due to difference in aneuploidy rates.

The chorionic cavity is the largest space inside the early human gestational sac and essential reservoir in the fetal nutrition pathway [37]. Up to the early second-trimester, the decidual glands secretion provide histiotrophic support and the placenta appears able to stimulate its own development by up-regulating gland activity in response to endocrine signals [38,39]. In normally implanted intrauterine human pregnancies, these glands open directly inside the intervillous space supplying the developing placenta with carbohydrate- and lipid-rich secretions and a variety of growth factors that may regulate placental morphogenesis [38,39]. The decidual transformation of the endometrium stroma occurs in the mid-luteal phase of the menstrual cycle, independently of pregnancy [40]. A thin endometrial thickness is associated with low pregnancy rates after IVF irrespective of the causing factor [41]. Endometrial gland secretions are equally, if not more, essential in other mammal species. For example, up to day 23 post-conception, the equine embryo floats in the uterine cavity, fed exclusively by the exocrine secretions of the endometrial glands [42]. Thus, when placentation occurs in a large cesarean scar with no or limited endometrial re-epithelisation [14], the decidual secretion from the uterine cavity above may be sufficient for the early development of a gestational sac. By contrast, when the blastocyst attaches and the placenta develops within a Fallopian tube, even if the intrauterine endometrium undergoes full decidualisation [40], the corresponding glands secretion are unlikely to reach the tubal gestational sac. This may explain the higher rate of gestational sac development 5th centile in both types of ectopic pregnancies (Table 1), difference in GSD patterns (Fig. 2) and the overall higher rate of early pregnancy failure in TEP compared to CSP (Table 2).

In placenta accreta spectrum (PAS), the extravillous trophoblast cells migrate from the placenta anchoring villi into the uterine wall through the entire depth of the myometrium, with some progressive degree of transformation of the deep arterial vasculature [16]. An increased vascularity in 98% of CSPs in the present study suggests that the vascular changes associated with abnormally deep placentation start in the first trimester. By contrast, in TEP, extravillous trophoblast cells penetrate the tubal wall [13], ultimately leading to its rupture. Significantly (P <.001) lower vascularity in TEP than in CSP, suggest that the biological impact of the extravillous trophoblast on the development of vasculature surrounding the Fallopian tube is limited (Fig. 1). A hemoperitoneum was recorded on transvaginal ultrasound examination in 30% of the tubal pregnancies in the present study. Unlike TEPs, CSPs are surrounded by thick myometrial layers and thus they rarely lead to uterine rupture during the first trimester of pregnancy. A recent systematic review and meta-analysis of the outcome of CSP managed expectantly has shown that those with a heartbeat are at higher risk of experiencing severe bleeding than those presenting without fetal heart activity (Cali et al., 2018). The data of the present study suggest that 2/3rds of live CSPs are likely to survive into the second trimester, with a higher risk of complications including uterine rupture, accreta placentation and major placenta previa. These finding highlights the need for a surgical evacuation procedure in most cases of CSP, even if the pregnancy stops developing.

In conclusion, tubal and cesarean scar ectopic pregnancies have different outcomes due to the different environment where they implant with < 10% of TEPs and around 1/3rd of CSPs presenting with a fetal cardiac activity at 6-11 weeks of gestation. The difference in miscarriage rate between the two types of ectopic pregnancies is probably due to an environmental factor rather than abnormal embryogenesis associated with aneuploidy or other genetic anomalies. TEPs develop in a location with limited access to histiotrophic support and are less likely to progress in the second trimester even in the presence of fetal heart rate activity. By contrast, CSPs develop close to the normal uterine environment and most will progress into the second trimester. Further research should look in the prospective role of ultrasound measurements and maternal serum biomarkers of placental function in the management of these pregnancies.

Declaration of competing interest

None.

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Table 1. Comparison of the maternal demographics and main ultrasound characteristics for the live tubal ectopic pregnancies (TEP) and for the live cesarean scar pregnancies (CSP).

Variables	**TEP (n= 69)**	**CSP (n=54)**	***P***
Maternal age (years)	32.0 (28.0;36.0)	35.0 (32.0;38.0)	.005¶
Gravidity	2.0 (1.0;3.0)	5.0 (3.0;6.0)	<.001¶
Parity	0.0 (0.0;1.0)	2.0 (2.0;3.0)	<.001¶
Symptoms			
- Bleeding (%)	11 (15.9%)	11 (20.4%)	
- Pain (%)	10 (14.5%)	7 (13.0%)	
- Bleeding and pain (%)	16 (23.2%)	21 (38.9%)	0.562*
Gestational age (days)	51.0 (44.0;57.0)	52.5 (46.0;66.0)	0.079¶
GSD (mm) $<5^{th}$ Centile (%)	58 (84.1%)	17 (31.5%)	<.001
CRL (mm) $<5^{th}$ Centile (%)	30 (43.5%)	16 (29.6%)	.115
FHR (bpm) $<5^{th}$ Centile (%)	20 (29.0%)	18 (33.3%)	.604
Yolk sac diameter (mm) $<5^{th}$ Centile (%)	13 (18.8%)	11 (20.4%)	.832
Yolk sac diameter (mm) $>95^{th}$ Centile (%)	7 (10.1)	8 (14.8%)	.617
Blood flow score			
- Minimal blood flow (%)	25 (36.2%)	1 (1.9%)	
- Moderate blood flow (%)	34 (49.3%)	31 (57.4%)	
- High vascularity (%)	10 (14.5%)	22 (40.7%)	<.001*

Numerical data are presented as median (interquartile range) and categorical data as n (%). ¶Mann-Whitney (Wilcoxon) W rank test; *Chi-square with Yates correction.
GSD: Gestational sac diameter; CRL: Crown-rump length; FHR: Fetal heart rate.

Table 2. Comparison of the ultrasound measurements in live tubal ectopic pregnancies (TEP) and live cesarean scar pregnancies (CSP) matched for gestational age.

Variables	**TEP (n= 40)**	**CSP (n=40)**	**P**
Gestational sac diameter (mm)	12.2 (9.0;19.1)	21.4 (12.4;25.3)	<.001
CRL (mm)	6.2 (3.0;10.4)	6.9 (3.7;12.4)	.378
CRL/Gestational sac diameter	0.52 (0.37;0.70)	0.37 (0.26;0.59)	.051
FHR (bpm)	128.0 (104.5;156.5)	118.5(100.0;152.0)	.274
Yolk sac diameter (mm)	3.9 (3.4;4.3)	3.7 (3.1;4.6)	.596

Data are presented as median (interquartile range) and compared with the Mann-Whitney (Wilcoxon) W rank test.
CRL: Crown-rump length; FHR: Fetal heart rate.

References

1. C.J. Elson, R. Salim, N. Potdar, M. Chetty, J.A. Ross, E.J Kirk; on behalf of the Royal College of Obstetricians and Gynaecologists Diagnosis and Management of Ectopic Pregnancy. B.J.O.G. 123 (2016) e15-e55.
2. ESHRE working group on Ectopic Pregnancy, E. Kirk, P. Ankum, A. Jakab, N. Le Clef, A. Ludwin, R. Small, T. Tellum, M. Töyli, T. Van den Bosch, D. Jurkovic. Terminology for describing normally sited and ectopic pregnancies on ultrasound: ESHRE recommendations for good practice. Hum. Reprod. Open. (2020). hoaa055. doi: 10.1093/hropen/hoaa055.
3. E. Jauniaux E, D. Jurkovic. Ectopic pregnancy: 130 years of medical diagnostic challenges. B.J.O.G. 125 (2018)1672.
4. A. Rempen, P. Albert. Diagnosis and therapy of and therapy of an early pregnancy implanted in the cesarean section scar. Z. Geburtshilfe Perinatol. 194 (1990) 46-48.
5. D. Jurkovic, K. Hillaby, B. Woelfer, A. Lawrence, R. Salim, C.J. Elson. First trimester diagnosis and management of pregnancies implanted into the lower uterine segment cesarean section scar. Ultrasound Obstet Gynecol 21 (2003) 220–227.
6. R. Maymon, R. Halperin, S. Mendlovic, D. Schneider, Z. Vaknin, A. Herman, M. Pansky. Ectopic pregnancies in Caesarean section scars: the 8-year experience of one medical centre. Hum. Reprod. 19 (2004) 278-284.
7. H.M. Harb, M. Knight, C. Bottomley, C. Overton, A. Tobias, I.D. Gallos, M. Shehmar, R. Farquharson, A. Horne, P. Latthe, D. Jurkovic. Caesarean scar pregnancy in the UK: a national cohort study. B.J.O.G.125 (2018) 1663-1670.

8. J. Ben Nagi, D. Ofili-Yebovi, M. Marsh, D. Jurkovic. First-trimester cesarean scar pregnancy evolving into placenta previa/accreta at term. J. Ultrasound. Med.24 (2005) 1569-1573.
9. I.E. Timor-Tritsch, A. Monteagudo. Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. Am. J. Obstet. Gynecol. 207 (2012) 14-29.
10. N. Zosmer, J. Fuller, H. Shaikh, J. Johns, J.A. Ross. Natural history of early first-trimester pregnancies implanted in Cesarean scars, Ultrasound Obstet. Gynecol. 46 (2015) 367-375.
11. G. Cali, F. Forlani, I.E. Timor-Tritsch, J. Palacios-Jaraquemada, G. Minneci, F. D'Antonio. Natural history of Cesarean scar pregnancy on prenatal ultrasound: the crossover sign, Ultrasound Obstet. Gynecol. 50 (2018) 100-104.
12. T. Boerma, C. Ronsmans, D.Y. Melesse, A.J.D Barros, F.C. Barros, L. Juan, A.B. Moller, L. Say, A.R. Hosseinpoor, M.Yi. Global epidemiology of use of and disparities in caesarean sections. Lancet. 392 (2018) 1341-1348.
13. S. Randall, C.H. Buckley, H. Fox. Placentation in the fallopian tube. Int. J. Gynecol. Pathol. 6 (1987) 132-139.
14. J. Ben-Nagi, A. Walker, D. Jurkovic, J. Yazbek, J.D. Aplin. Effect of cesarean delivery on the endometrium. Int. J. Gynaecol. Obstet. 106 (2009) 30-34.
15. H.A. Roeder, S.F. Cramer, P.C. Leppert. A look at uterine wound healing through a histopathological study of uterine scars. Reprod. Sci. 19 (2012) 463-473.
16. E. Jauniaux, N. Zosmer, D. Subramanian, H. Shaikh, G.J. Burton. Ultrasound-histopathologic features of the utero-placental interface in placenta accreta spectrum. Placenta. 97 (2020) 58-64.

17. G.I. Papaioannou, A. Syngelaki, L.C. Poon, J.A. Ross, K.H. Nicolaides. Normal ranges of embryonic length, embryonic heart rate, gestational sac diameter and yolk sac diameter at 6-10 weeks. Fetal. Diagn. Ther. 28 (2010) 207-219.
18. D. Timmerman, L. Valentin, T.H. Bourne, W.P. Collins, H. Verrelst, I. Vergote; International Ovarian Tumor Analysis (IOTA) Group. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. Ultrasound Obstet. Gynecol. 16 (2000) 500-505.
19. A.J. Wilcox, C.R. Weinberg, J.F O'Connor, D.D. Baird, J.P Schlatterer, R.E Canfield, E.G Armstrong, B.C Nisula. Incidence of early loss of pregnancy. N. Engl. J. Med. 319 (1988) 189–194.
20. M.J. Zinaman, E.D. Clegg, C.C. Brown, J. O'Connor, S.G. Selevan. Estimates of human fertility and pregnancy loss. Fertil. Steril. 65 (1996) 503–509.
21. A. Nazari, J.H. Check, R.H Epstein, C. Dietterich, S. Farzanfar. Relationship of small-for-dates sac size to crown-rump length and spontaneous abortion in patients with a known date of ovulation. Obstet. Gynecol. 78 (1991) 369-373.
22. B. Bromley, B.L. Harlow, L.A. Laboda, B.R. Benacerraf. Small sac size in the first trimester: a predictor of poor fetal outcome. Radiology. 178 (1991) 375-377.
23. J.S. Oh, G. Wright, C.B. Coulam. Gestational sac diameter in very early pregnancy as a predictor of fetal outcome. Ultrasound Obstet. Gynecol.20 (2002)267-269.
24. G. Makrydimas, N.J. Sebire, D. Lolis, N. Vlassis, K.H. Nicolaides. Fetal loss following ultrasound diagnosis of a live fetus at 6-10 weeks of gestation. Ultrasound Obstet. Gynecol. 22 (2003) 368-372.
25. J.D. Kapfhamer, S. Palaniappan, K. Summers, K. Kassel, A.C. Mancuso, G.L. Ryan, D.K. Shah. Difference between mean gestational sac diameter and crown-

rump length as a marker of first-trimester pregnancy loss after in vitro fertilization. Fertil. Steril. 109 (2018) 130-136.

26. L. Detti, L. Francillon, M.E. Christiansen, I. Peregrin-Alvarez, P.J. Goeske, Z. Bursac, R.A. Roman. Early pregnancy ultrasound measurements and prediction of first trimester pregnancy loss: A logistic model. Sci. Rep. 10 (2020) 1545.

27. A. Idelson, H. Meiri, A. Wertheimer, M. Sammar, K. Tenenbaum-Gavish, Y. Shufaro, A. Ben-Haroush. New predictors of early impaired placentation preceding miscarriage before 10 weeks of gestation in IVF pregnancies: A prospective study. Placenta. 100 (2020) :30-34.

28. R. Achiron, O. Tadmor, S. Mashiach. Heart rate as a predictor of first-trimester spontaneous abortion after ultrasound-proven viability. Obstet. Gyneco. 78 (1991) 330-334.

29. F.K. Varelas, N.M. Prapas, R.I. Liang, I.M. Prapas, G.A. Makedos. Yolk sac size and embryonic heart rate as prognostic factors of first trimester pregnancy outcome. Eur. J. Obstet. Gynecol. Reprod. Biol. 138 (2008) 10-13.

30. D.M. Berdahl, J. Blaine, B. Van Voorhis, A. Dokras. Detection of enlarged yolk sac on early ultrasound is associated with adverse pregnancy outcomes. Fertil. Steril. 94 (2010) 1535-1537.

31. L. Detti, R.A. Roman, P.J Goedecke, M.E Christiansen, I. Peregrin-Alvarez, G. Ikwuezunma, L. Francillon. Pilot study establishing a nomogram of yolk sac growth during the first trimester of pregnancy. J. Obstet. Gynaecol. Res. 46 (2020) 223-228.

32. A.M Nybo Andersen, J. Wohlfahrt, P. Christens, J. Olsen, M. Melbye. Maternal age and fetal loss: population based register linkage study. B.M.J. 320 (2000) 1708–1712.

33. T. Bessho, H. Sakamoto, T. Shiotani, S. Komori, K. Koyama. Fetal loss in the first trimester after demonstration of cardiac activity: relation of cytogenetic and ultrasound findings. Hum. Reprod. 10 (1995) 2696-2699.
34. L. Sagi-Dain, A. Peleg, S. Sagi. First-trimester crown-rump length and risk of chromosomal aberrations - A systematic review and meta-analysis. Obstet. Gynecol. Surv. 72 (2017) 603-609.
35. S. Elias, M. LeBeau, J.L. Simpson, A.O Martin. Chromosome analysis of ectopic human conceptuses. Am. J. Obstet. Gynecol. 141 (1981) 698–703.
36. S. Toikkanen, H. Joensuu, R. Erkkola R. DNA aneuploidy in ectopic pregnancy and spontaneous abortions. Eur. J. Obstet. Gynecol. Reprod. Biol. 51 (1993) 9–13.
37. E. Jauniaux, B. Gulbis. Fluid compartments of the embryonic environment. Hum. Reprod. Update. 6 (2000) 268-278.
38. G.J Burton, E. Jauniaux, D.S. Charnock-Jones. Human early placental development: potential roles of the endometrial glands. Placenta. 28 Suppl. A (2007) S64-69.
39. G.J Burton, E. Jauniaux, D.S. Charnock-Jones. The influence of the intrauterine environment on human placental development. Int. J. Dev. Biol. 54 (2010) 303-312.
40. W.C. Duncan, J.L. Shaw, S. Burgess, S.E McDonald, H.O Critchley, A.W. Horne. Ectopic pregnancy as a model to identify endometrial genes and signaling pathways important in decidualization and regulated by local trophoblast. PLoS. One. 6(2011) e23595.
41. N Mahajan, S. Sharma. The endometrium in assisted reproductive technology: How thin is thin? J. Hum. Reprod. Sci. 9 (2016) 3-8.
42. C.J.P Jones, J.D. Aplin, W.R.T. Allen, S. Wilsher. The influences of cycle stage and pregnancy upon cell glycosylation in the endometrium of the mare. Theriogenology. 154 (2020) :92-99.

43. G. Calì, I.E. Timor-Tritsch, J. Palacios-Jaraquemada, A. Monteaugudo, D. Buca, F. Forlani, A. Familiari, G. Scambia, G. Acharya, F. D'Antonio. Outcome of Cesarean scar pregnancy managed expectantly: systematic review and meta-analysis. Ultrasound. Obstet .Gynecol. 51 (2018) 169-175.

Figure legends

Figure 1. Diagram illustrating a tubal and cesarean scar ectopic pregnancy and the corresponding 3D and CDI view.
a & b: Tubal ectopic pregnancy at 8 weeks + 6 days showing a minimal blood flow;
c & d: Cesarean scar ectopic pregnancy at 9 weeks + 6 days showing hypervascularity.
U= Uterus; GS= Gestational sac; Cx= Cervix.

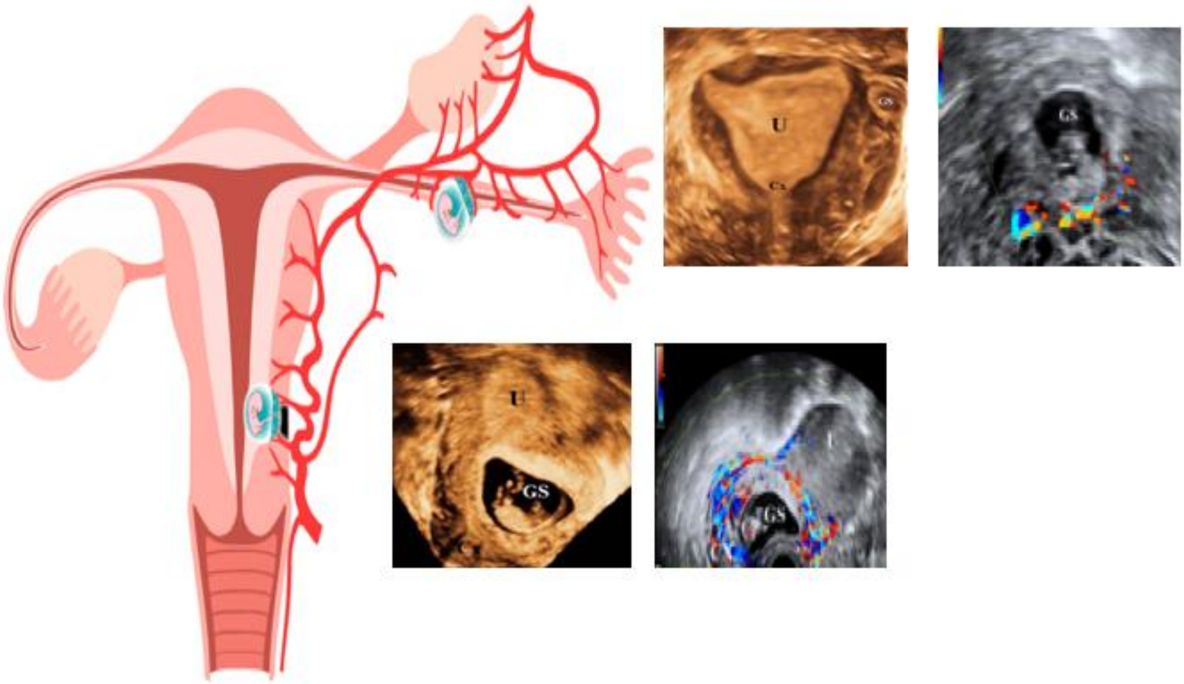


Figure 2. Scatterplots of mean gestation sac diameter (mm) vs. time (days) with regression line fit and 95% confidence intervals for: Tubal ectopic pregnancies (R^2 =0.3410) and Cesarean scar pregnancies (R^2 =0.5545).

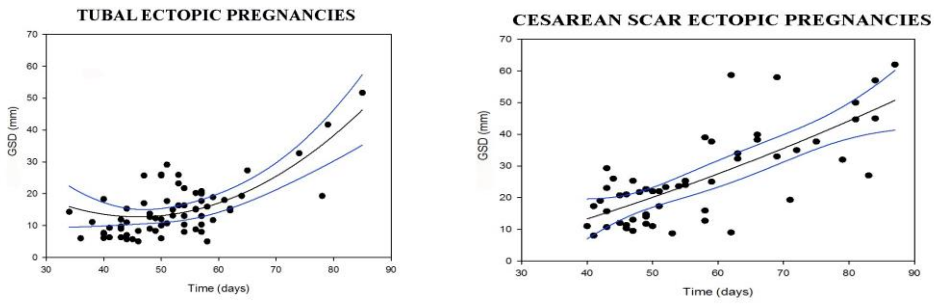
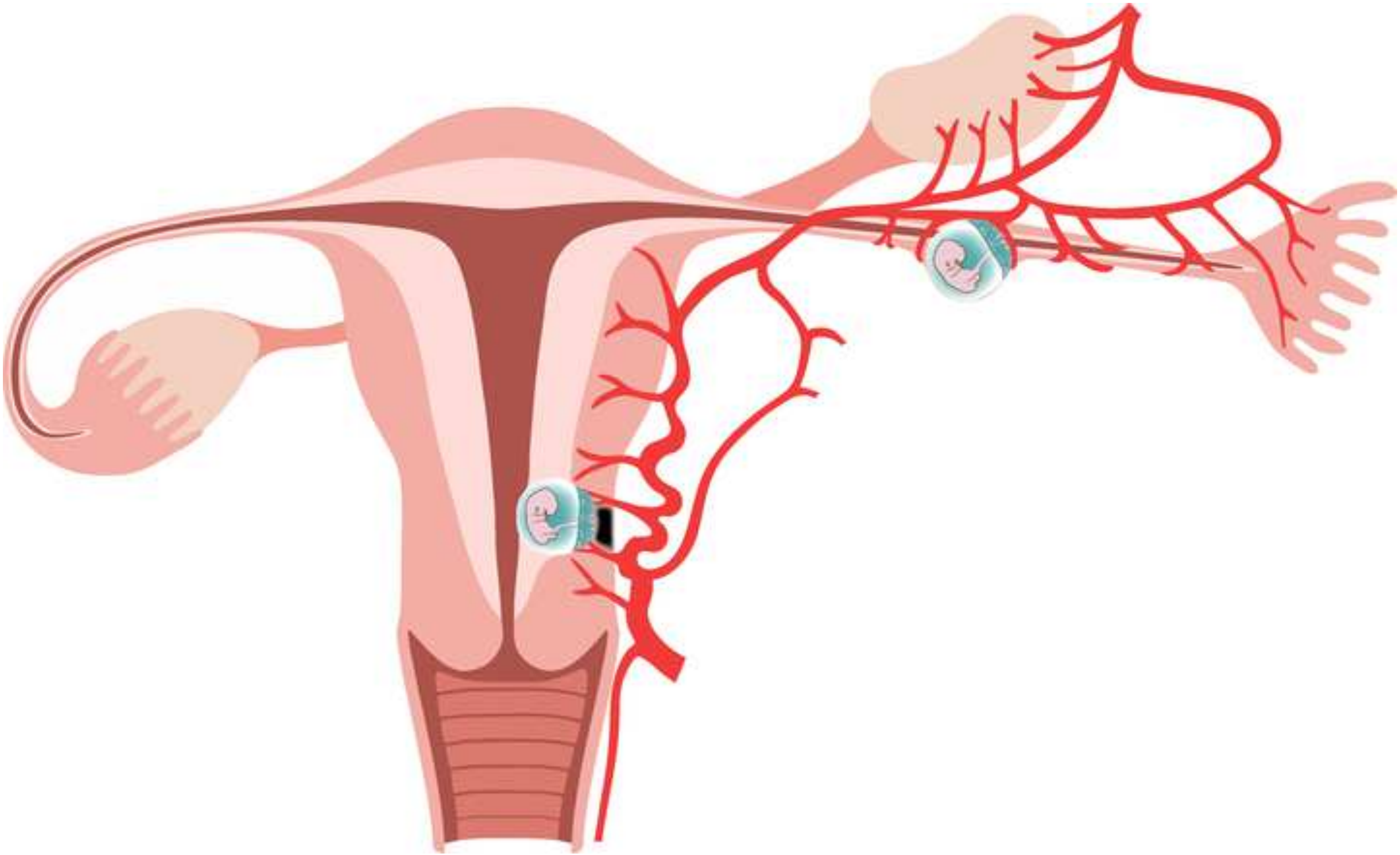


Figure 1 Diagram




GS
U
Cx
a

Figure 1b

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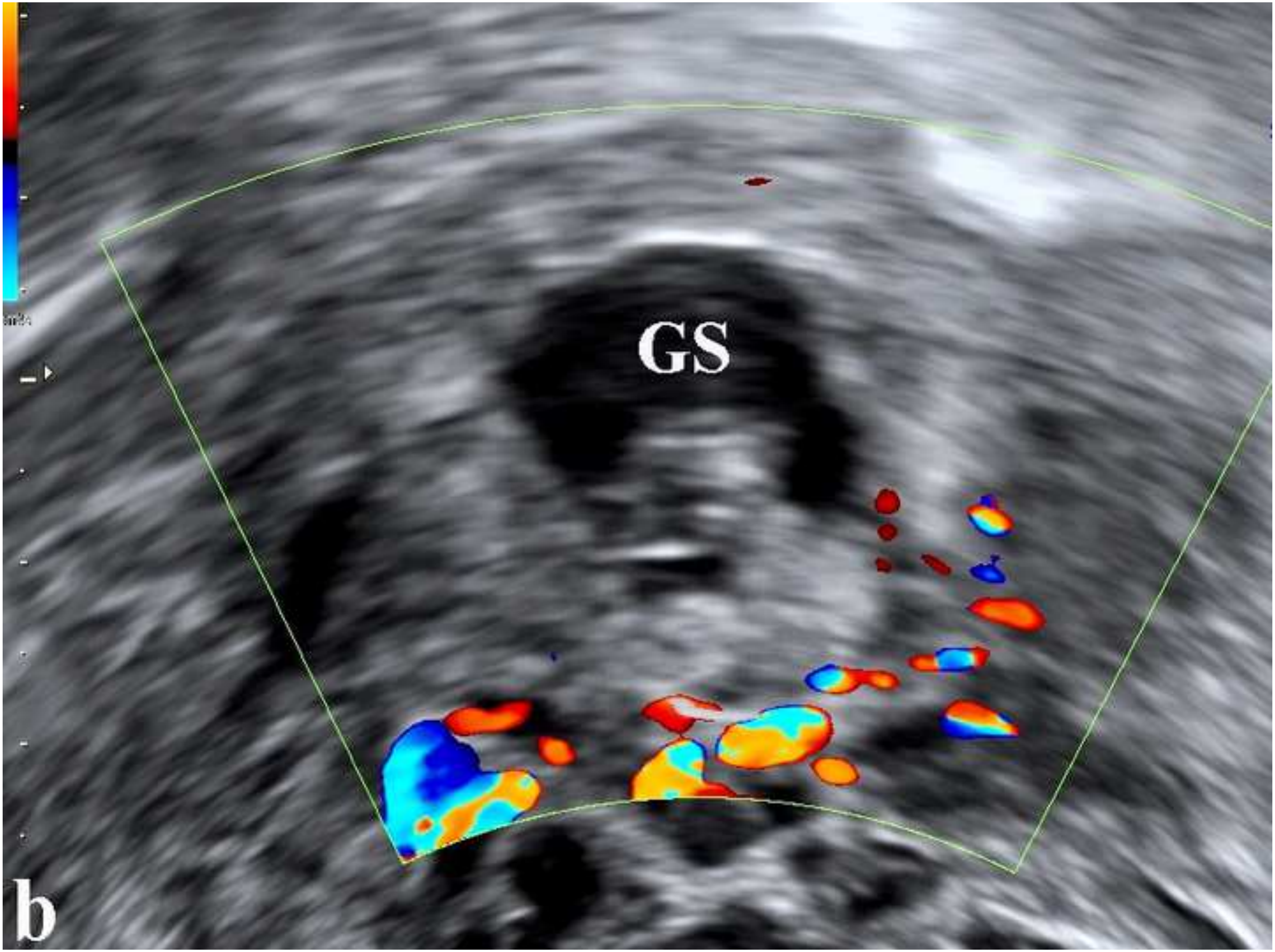

Figure 1c

Figure 1d

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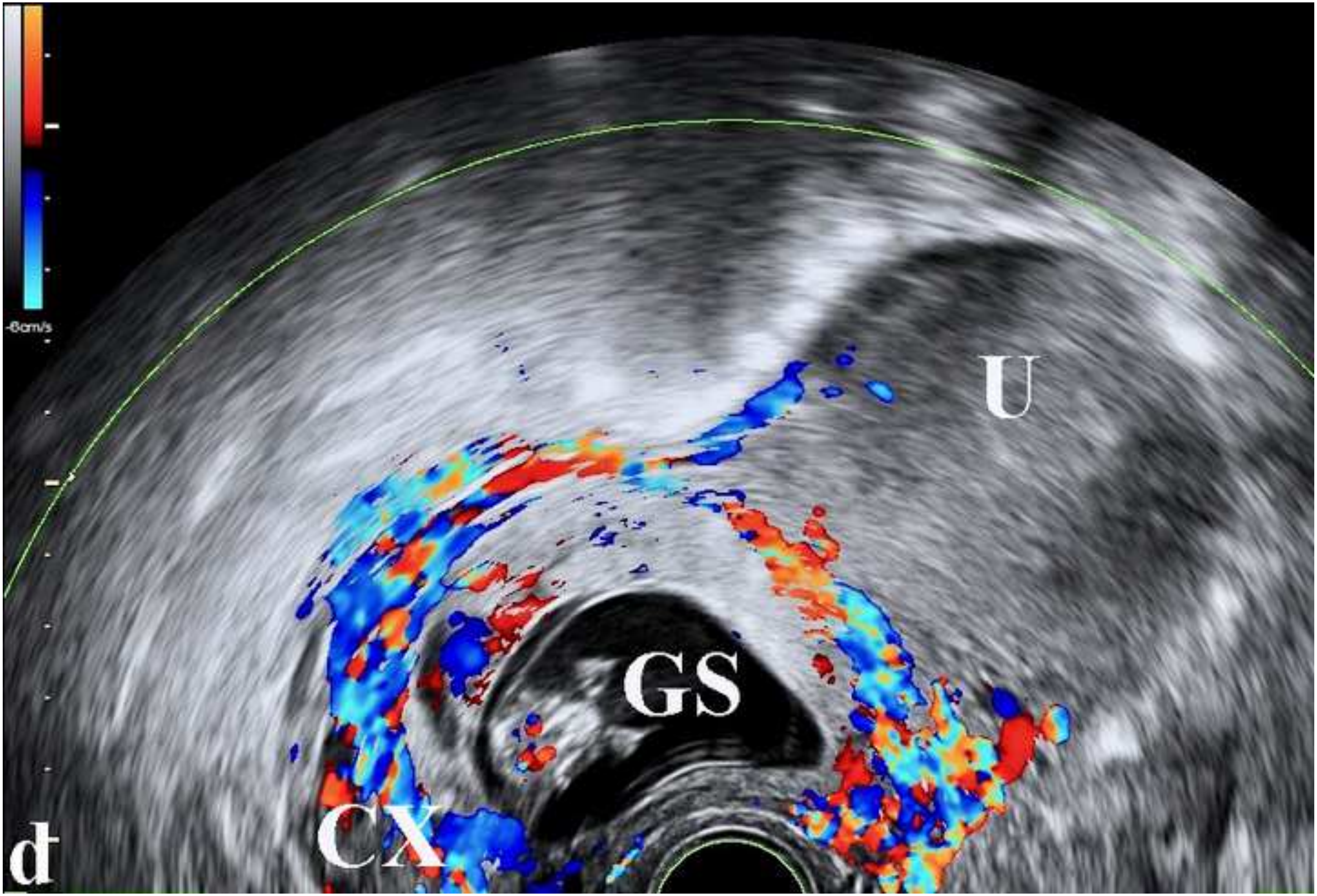

Figure 2 TEP

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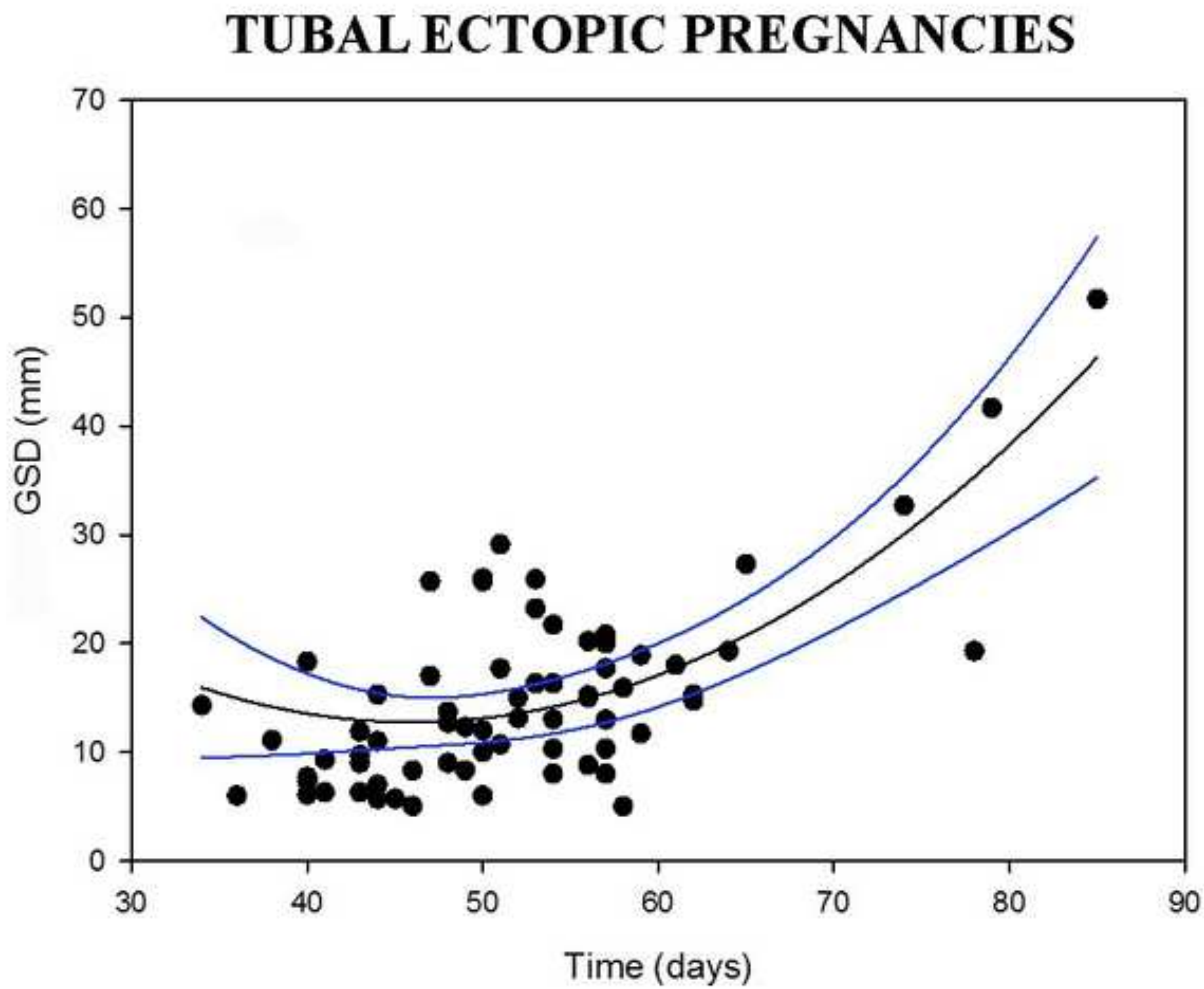

Figure 2 CSP

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